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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/809,158	COWING, CAROL O.	
	Examiner	Art Unit	
	Karen A. Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,4-11,13-19,21-24,27-31,37,42,51-55,58 and 59 is/are pending in the application.

4a) Of the above claim(s) 4,5,7,9,10,37,42 and 59 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,6,8,11,13-19,21-24,27-31,51-55 and 58 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/22/2004.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

1. The text of sections of Title 35, US Code not found in this action can be found in a previous Office action.

2. Claims 17, 19, 23, 24, 52, 55 and 58 have been amended. Claim 56 has been canceled. Claims 1, 4-11, 13-19, 21-24, 27-31, 37, 42, 51-55, 58 and 59 are pending. Claims 4, 5, 7, 9, 10, 37, 42 and 59 remain withdrawn from consideration. Claims 1, 6, 8, 11, 13-19, 21-24, 27-31, 51-55 and 58 are under consideration.

3. The rejection of claim 30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The rejection of claim 31 has been withdrawn in light of applicants arguments. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Claim 30 embodies the method of claim 1 wherein the amount of topical treatment is further characterized as being sufficient to increase the local release of an endogenous inducer of dendritic cell migration and maturation. The instant claims are reliant upon the identity of the endogenous inducer of dendritic cell migration and maturation and the plasma membrane expression of an adhesion molecule. The specification dose not describe the structure of either of the endogenous inducer of dendritic cell migration and maturation, nor the expression of the adhesion molecule. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or

"mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. thus the specification lacks an adequate written description for the endogenous inducer of dendritic cell migration and maturation and the adhesion molecule which is expressed on the plasma membrane. Because the specification lacks adequate written description of these products, it also lacks adequate written description for method claims reliant upon the identity of said products.

Applicant argues that the specification provides a sufficient list of inducers of dendritic cell migration and maturation and adhesion molecules to show possession of the claimed methods. This has been considered and found persuasive in part. Applicant provided page and line numbers to support this allegation. Upon review of said text, it is noted that although intercellular adhesion molecules are upregulated during dendritic cell maturation there is no mention of a specific endogenous inducer of dendritic cell migration and maturation. The claim as such reads on an endogenous inducer of dendritc cell migration and maturation which is not a known molecule.

4. The rejection of claims 1, 6, 8, 11, 13, 14, 16 and 28-31under 35 U.S.C. 102(b)as being anticipated by Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30) is maintained for reasons of record.

Dearman et al disclose a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al disclose that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of

cell-assoicated antigen. Dearman et al disclose that this phenomenon is consistent with a vigorous stimulation of the cutaneous immune response. Dearman et al disclose that the results imply that exposure of FITC in acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of FITC antigen by Langerhans cells is enhanced. Thus, Dearman et al disclose the specific limitation of increasing the number of antigen bearing dendritic cells in a draining lymphoid organ. (page 29, first column, line 2 to second column, line 7).

5. The rejection of claims 1, 6, 8, 11, 13, 14, 16, 17, 21, 22, 27, 28, 29, 30, 31 and 51 are rejected under 35 U.S.C. 103(a)as being unpatentable over Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30) in view of Mitragotri et al (WO 97/04832) and Paul et al (Vaccine Research, 1995, Vol. 4, pp. 145-164, cited in a previous action) is maintained for reasons of record.

The specific embodiments of claims 1, 6, 8, 11, 13, 14, 16, 28, 29, 30, 31, 55, and 56 are et forth above. Claim 17 is drawn to a method for vaccinating a mammal against an antigen comprising introducing into the mammal an effective dose of the antigen or an epitope thereof and administering to the mammal a topical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells in a lymphoid organ, wherein introducing the antigen and administering the treatment are performed independently in any order and wherein he topical treatment comprises application of ultrasound energy.

Dearman et al teach a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al teach that lymph node activation during the induction phase of contact sensitization and the stimulation of Langerhans cell proliferative responses are dependent upon the arrival within the draining lymph nodes of immunostimulatory antigen-bearing dendritic cells (page 26, , lines 1-4 under the heading "Dendritic Cell Accumulation in Draining Lymph Nodes"). Dearman et al teach that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of cell-assoicated antigen. Dearman et al teach that this phenomenon is consistent with a vigorous stimulation of the cutaneous immune response. Dearman et al teach that exposure to FITC in

acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of FITC antigen by Langerhans cells is enhanced. Dearman et al do not teach a method of topical immunization wherein the antigen was an endogenous protein, or a method of topical immunization where the antigen was injected into the epidermis,

Paul et al disclose a method for vaccinating a mammal against an antigen comprising the topical administration of an antigen encapsulated in tranfersomes. Paul et al disclose that the encapsulated protein traverses the stratum corneum by means of the ultradeformable submicroscopic transfersome vesicles (page 147, fourth full paragraph). Paul et al do not teach a method of immunization comprising a lipophilic molecule, or a method of increasing the number of antigen-bearing dendritic cells in a draining lymph node

Mitragotri et al teach that the passive skin permeability to high molecular weight proteins is essentially zero (page 29, line 35 to page 30, line 2). Mitragotri et al teach that ultrasound application induces significant transdermal permeation of large proteins such as insulin, gamma interferon and erythropoietin (page 21, lines 3-5). Mitragrti et al teach that high molecular weight proteins can be encapsulated in liposomes which are coated with lipophilic molecules in order to enhance penetration (page 23, lines 3-6 and page 23, line 21 to page 4, line 5).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer an endogenous protein antigen by means of intraepidermal or intradermal injection, ultrasound or ultrasound of encapsulated protein molecules, wherein the capsule is coated with lipophilic molecules, and wherein dibutyl phthalate was applied to the skin either before or after said ultrasound treatment. One of skill in the art would be motivated to do so by the teachings of Dearman et al on the independent action of dibutyl phthalate on the acquisition of antigen by dendritic cells within draining lymph nodes wherein said antigen is delivered to the lymph nodes via Langerhans cells and the teachings of Mitragotri et al on the lack of penetration of large proteins into the stratum corneum without use of ultrasound or ultrasound in combination with encapsulated proteins. One of skill in the art would conclude that direct intraepidermal or intradermal injection of the protein antigen would be an alternative for the ultrasound permeation because it would place the protein antigen in proximity to

Langerhans cells and thus would result in the transport of the antigen to the draining lymph nodes.

6. The rejection of claims 1, 18 and 24 under 35 U.S.C. 103(a) as being unpatentable over Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30) in view of King et al (Vaccine, 1987, Vol. 5, pp. 234-238, cited in a previous action) is maintained for reasons of record.

Claim 24 is drawn to a method for vaccinating a mammal against an antigen comprising administering to the mammal an effective dose of an antigen or epitope thereof and a topical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells, wherein the antigen and the topical treatment are performed independently in any order wherein said topical treatment comprises a lipophilic molecule capable of traversing the stratum corneum and inducing dendritic cells to migrate to the draining lymph nodes and wherein the antigen or epitope thereof is introduced into the mammal by a transfer of cells containing the antigen or epitope thereof. Claim 18 embodies the method of claim 1 wherein the antigen or epitope thereof is introduced into the mammal by a virus, bacterium , fungus or parasite.

Dearman et al teach a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al teach that lymph node activation during the induction phase of contact sensitization and the stimulation of Langerhans cell proliferative responses are dependent upon the arrival within the draining lymph nodes of immunostimulatory antigen-bearing dendritic cells (page 26, , lines 1-4 under the heading "Dendritic Cell Accumulation in Draining Lymph Nodes"). Dearman et al teach that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of cell-assoicated antigen. Dearman et al teach that this phenomenon is consistent with a vigorous stimulation of the cutaneous immune response. Dearman et al teach that exposure to FITC in acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of FITC antigen by Langerhans cells is enhanced. Dearman et al do not teach a method of topical

immunization wherein the antigen was introduced into the mammal by a transfer of cells containing the antigen or epitope thereof.

King et al disclose a method for vaccinating a mammal against an antigen comprising delivering to the nasal passages a topically applied live vaccine, thus fulfilling he specific embodiment of claim 18.

It would have been prima facie obvious at the time the invention was made to administer topical dibutyl phthalate either before or after the administration of the cellular vaccine of King et al. One of skill in the art would be motivated to do so by the teachings of Dearman et al on the increase in antigen-bearing dendritic cells in the draining lymph nodes observed after topical administration of dibutyl phthalate.

7. The rejection of claims 19 and 23 under 35 U.S.C. 103(a) as being unpatentable over Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30) in view of Salyers et al (Bacterial Pathogenesis (text), 1994, pp. 8-14 and 144-145) is maintained for reasons of record.

Claim 19 is drawn to a method for vaccinating a mammal against an antigen comprising introducing into the mammal an effective dose of the antigen or an epitope thereof and administering to the mammal a optical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells in a lymphoid organ, wherein introduction of the antigen is carried out by ingestion. Claim 23 embodies the method of claim 1 wherein the antigen or epitope thereof is introduced into the mammal via delivery to the gastrointestinal tract.

Dearman et al teach a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al teach that lymph node activation during the induction phase of contact sensitization and the stimulation of Langerhans cell proliferative responses are dependent upon the arrival within the draining lymph nodes of immunostimulatory antigen-bearing dendritic cells (page 26, , lines 1-4 under the heading "Dendritic Cell Accumulation in Draining Lymph Nodes"). Dearman et al teach that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of cell-assoicated antigen. Dearman et al teach that this phenomenon is consistent with a vigorous

stimulation of the cutaneous immune response. Dearman et al teach that exposure to FITC in acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of FITC antigen by Langerhans cells is enhanced. Dearman et al do not teach a method of topical immunization wherein the antigen was introduced into the gastrointestinal tract by ingestion.

Saylers et al teach the colonization of the mucosal epithelium by natural pathogens (pages 144-145). Saylers et al teach that mucosal membranes of the intestinal tract have specialized mucosal assoicated lymphoid tissues for defense against ingested bacteria and other antigens (page 9, first column, first full paragraph). It would be prima facie obvious to one of skill in the art that an antigen can be introduced into a mammal by ingestion, and that one could increase the number of antigen bearing dendritic cells within a draining lymph node by topical administration of dibutyl phthalate. One of skill in the art would be motivated to do so by the teachings of Dearman et al on the induction of greater numbers of antigen-bearing dendritic cells within draining lymph nodes.

8. The rejection of claims 1, 6, 8, 11, 13-16, 27, 28-31, 52, 53, 55 and 58 under 103(a) Dearman et al (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30) in view of Glenn et al (US 5,980,898, cited in a previous action) is maintained of reasons of record.

Dearman et al teach a method of topical immunization comprising the administration of FITC in acetone solutions comprising dibutyl phthalate. Dearman et al teach that lymph node activation during the induction phase of contact sensitization and the stimulation of Langerhans cell proliferative responses are dependent upon the arrival within the draining lymph nodes of immunostimulatory antigen-bearing dendritic cells (page 26, , lines 1-4 under the heading "Dendritic Cell Accumulation in Draining Lymph Nodes"). Dearman et al teach that although DBP did not have an influence on the numbers of dendritic cells reaching the lymph nodes DBP markedly increased the proportion of dendritic cells bearing antigen and the median amount of cell-assoicated antigen. Dearman et al teach that this phenomenon is consistent with a vigorous stimulation of the cutaneous immune response. Dearman et al teach that exposure to FITC in acetone results in the migration of Langerhans cells from the skin and the accumulation of dendritic cells in draining nodes, but that in the presence of dibutyl phthalate the acquisition of

FITC antigen by Langerhans cells is enhanced. Dearman et al do not teach a method of topical immunization wherein the antigen was

Glenn et al disclose a method for vaccinating a mammal comprising the topical administration of an antigen such as a tumor antigen (column 3, lines 64-67 and column 15, lines 52-67) in a composition comprising an activator of Langerhans cells, wherein said activators include trinitrochlorobenzene, dinitrofluorbenzene, pentadecylcatecol and lipid A (column 11, lines 31-40), thus fulfilling the specific embodiments of a lipophilic molecule having a molecular weight less than or equal to 500 Daltons and an internal administration to the skin as an organ, thus fulfilling the specific embodiment of claim 56, drawn to delivery into an organ. Glenn et al do not specifically teach embodiments of claim 58 drawn to increasing the number of antigen-bearing dendritic cells in a draining lymphoid organ it would be inherent in the method of Glenn et al that said dendritic cells would be increased.

Applicant argues that the instant claims require the introduction of the antigen into the mammal by the disruption of the stratum corneum, and that Dearman et al fails to teach this limitation. Applicant argues that Mitragotri et al teaches against the claimed invention because Mitragotri et al teach the transport across intact skin using ultrasound. Applicant argues that Paul does not teach the limitation of introduction of the antigen by disruption of the stratum corneum because Paul et al teach the use of submicroscopic transfersome vesicles. This has been considered but not found persuasive. Page 22, line 19 to page 23, line 29 state that lipophilic solvents, low frequency ultrasound, electroporation, iontophoresis and intradermal delivery are all methods for the penetration of the stratum corneum. The penetration of the stratum corneum would be the same as the disruption of the stratum corneum. The specification does not teach a specific means to "disrupt" the stratum corneum which is not use of lipophilic solvents, low frequency ultrasound, electroporation, iontophoresis and intradermal delivery. Thus, applicant is arguing a meaning for the term "disruption" of the stratum corneum which is not supported by the specification. The use of dibutylphlalate in acetone as taught by Dearman et al is the same as the lipophilic solvents taught by the instant specification. The transport across intact skin as taught by Mitragotri et al using ultrasound is specifically taught by the specification. The

argument against the method of Paul is moot because Paul et al is not relied upon for the method of introducing the antigen in the reasons of record.

Applicant argues that Dearman in view of Salyers et al teaches away from the instant invention when the antigen is introduced into a mammal by ingestion. This has been considered but not found persuasive. Claims 19 and 23 do not require that the dibutlyphthalate and the antigen be introduced by the same route of administration. Dearman et al is relied upon for teaching regarding dibutylphthalate and Salyers et al is relied upon for teachings regarding the oral introduction of an antigen.

Applicant argues that Glen does not teach the instant invention because lipid A is 1.9KDa rather than less than 500 Da. This has been considered but not found persuasive. Glenn et al also teach trinitrochlorobenezene, dinotrofluorbenezene and pentadecylcatecol all which have molecular weights below 500Da and are lipophillic agent. Glenn et al teach the use of a penetration enhancer such as Aquaphor, anhydrous lipids, fats, waxes, oil, silicones and humectants which would be a lipophilic penetrant as taught by the specification. Applicant argues that there are not teaching to suggest the administration of a lipohilic agent which is not in combination with an antigen. This has been considered but not found persuasive. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant argues that claims 55 and 58 require the injection of the antigen into the mammal, and both Dearman et al and Glenn et al teach against this embodiment. This has been considered but not found persuasive. IT is well known in the art that a vaccine can be introduced into a mammal by injection. This is exemplified by the teachings of Glenn et al who state that "For previous vaccines, their formulation were injected through the skin with needles". Thus one of skill in the art would be cognizant of this method of introducing antigen.

9. The rejection of the claims1, 6, 8, 11, 13-19, 21-24, 27-31, 51-53, 55, 56 and 58 under the judicially created doctrine of obviousness-type double patenting over claims 1-21 of US patent

6,210,672 is maintained for reasons of record. Acknowledgment is made of applicants intention of filing a terminal disclaimer at the time allowable subject matter is indicated.

10. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants arguments and amendments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828.

Karen A. Canella, Ph.D
3/7/2005

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER